Vancomycin mic changes in methicillin-resistant staphylococcus aureus (MRSA) blood culture isolates

Metisiline dirençli staphylococcus aureus (MRSA) kan kültür izolatlarında vankomisin mik değişimleri

Malignant nodular hidradenoma of scalp

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Öz

Amaç: Staphylococcus aureus (S. aureus) suşlarında giderek artan sıklıkta, glikopeptid antibiyotiklere değişik derecelerde azalmış duyarlılık gözlenmektedir. Bu çalışmada, 2012-2015 yılları arasında hastanemizde, kan kültürlerinden izole edilen Metisiline dirençli S. aureus (MRSA) suşlarında Vankomisin minimum inhibitör konsantrasyon (MİK) değerlerinin belirlenmesi ve Vankomisin MİK değerlerinin yıllar içindeki (2007-2015) değişiminin değerlendirilmesi amaçlanmıştır. Gereç ve Yöntem: Çalışmaya, 2012-2015 yılları arasında kan kültürlerinden izole edilen toplam 45 MRSA suşu dahil edilmiştir. Vankomisin MİK değerleri E test yöntemi kullanılarak belirlenmiştir. Her yıl için, Vankomisin ortalama MİK ve geometrik ortalama MİK hesaplanmış ve yıllar arasındaki farklar analiz edilmiştir. Bu sonuçlar daha sonra, 2007 ile 2011 yılları arasında gerçekleştirilen önceki çalışmamızın sonuçları ile birlikte değerlendirilmiştir. Bulgular: İzolatlar arasında, Vankomisine dirençli S. aureus (VRSA) veya Vankomisine orta duyarlı S. aureus (VISA) izolatı saptanmamıştır. Sadece bir izolat heterojen VISA (hVISA) olarak değerlendirilmiştir. Ortalama MİK değerleri karşılaştırıldığında yıllar arasında (2012-2015) anlamlı fark bulunmuş (p=0,027) ve yıllara göre izlenen artış eğiliminin de anlamlı olduğu saptanmıştır (p=0,005). Her iki çalışmanın sonuçları birlikte değerlendirildiğinde; ortalama MİK değerleri açısından yıllar arasında (2007-2015) arasında anlamlı fark olduğu saptanmış (p=0,001) ve Vankomisin ortalama MİK değerlerinde, yıllar içinde izlenen artış eğiliminin de anlamlı olduğu görülmüştür (p<0,001). Tartışma: Sonuç olarak, bu çalışma ile hastanemizde MRSA kan kültürü izolatlarında Vankomisin MİK değerlerinin yıllar içinde artış gösterdiği gözlenmiştir. İnvaziv MRSA izolatlarında, Vankomisin MİK değerlerinin her merkezde sistematik olarak izlenmesi önem taşımaktadır.

Anahtar Kelimeler

Metisiline Dirençli Staphylococcus Aureus; MİK Creep; Minimum İnhibitör Konsantrasyon; Vankomisin

Abstract

Aim: Various levels of reduced susceptibility to glycopeptides are emerging with increasing frequency in Staphylococcus aureus (S. aureus) strains. We aimed to determine Vancomycin minimum inhibitory concentration (MIC)s for Methicillin-resistant S. aureus (MRSA) strains isolated from blood cultures between 2012-2015 and to evaluate changes in Vancomycin MIC levels over the years (2007-2015) at our institution. Material and Method: A total of 45 MRSA blood culture isolates between 2012 and 2015 were studied. MIC determinations for Vancomycin were performed using Etest method. The mean MIC and geometric mean MIC were calculated for each year and the differences between the years were analyzed. These results were then evaluated together with the results of our previous study performed between 2007 and 2011. Results: There was no Vancomycin-resistant S. aureus (VRSA) or Vancomycin-intermediate S. aureus (VISA) among the isolates. Only one strain was evaluated as hetero-resistant Vancomycin-intermediate S. aureus (hVISA). When compared, there were significant differences between the years (2012-2015) for the mean MICs (p=0.027) and the trend in the increase in the Vancomycin mean MICs over the years was found to be significant (p=0.005). When the results of both studies were evaluated together, there were significant differences between the years (2007-2015) for the mean MICs (p=0.001) and the upward trend in the Vancomycin mean MICs over the years was found to be significant (p<0.001). Discussion: We observed an increase in Vancomycin MICs for MRSA blood culture isolates over the years at our hospital. It is important to monitor local Vancomycin MICs in invasive MRSA isolates systematically.

Keywords

Methicillin-Resistant Staphylococcus Aureus; MIC Creep; Minimum inhibitory Concentration; Vancomycin

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Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) is a significant cause of both health care and community-acquired infections [1]. Although there are relatively stable or even decreasing rates in Europe and the United States, MRSA remains a major public health problem worldwide [2].

Vancomycin has been the mainstay of therapy for serious MRSA infections for decades. Although Vancomycin resistance (Vancomycin-resistant S. aureus, VRSA; MIC, ≥16 µg/mL) remains a remarkably rare phenomenon, and Vancomycin-intermediate S. aureus (VISA; MIC, 4-8 µg/mL) is not common, its role in the management of serious infections is now being reconsidered due to its limitations which include relatively slow bactericidal activity, therapeutic failure with the emergence of resistant strains and, possible "MIC creep" among susceptible strains [1, 3]. "MIC creep" is defined as the gradual increase in MICs to Vancomycin amongst susceptible S. aureus strains which is significantly associated with mortality particularly in bacteremic patients [2].

Another resistance phenotype, heterogenous-VISA (hVISA), refers to a strain of S. aureus that has a Vancomycin minimum inhibitory concentration (MIC) within the susceptible range when tested by routine methods but where a resistant subpopulation with a higher MIC (MIC, >2 µg/mL) at a frequency of 1/106 is present [4]. There are no prospective controlled studies that show the effect of hVISA on the patient's treatment success, and it is generally reported that hVISA does not increase mortality. However, it may cause increased lengths of stay and prolonged therapy due to Vancomycin treatment failure [5]. The prevalence of hVISA in MRSA strains isolated from blood was found to be 9.81% [6]. In a multicenter study, the reported rate was 13.7% in our country [7].

In this study we aimed to determine the Vancomycin MICs of MRSA strains isolated from blood cultures between 2012-2015 in Akdeniz University Hospital and to evaluate changes in Vancomycin MIC levels over the years (2007-2015) at our institution, by analyzing recent results in conjunction with the results of our previous study performed between 2007 and 2011.

Material and Method

A total of 45 MRSA strains which were isolated from blood cultures in Akdeniz University Hospital Microbiology Laboratory between 2012 and 2015 were included in the study. All isolates were identified as S. aureus by conventional standardized laboratory methods (e.g., Gram stain, catalase and tube coagulase tests) and by Bruker MALDI-TOF-MS (Bruker Daltonik, Germany) system. MRSA isolates were detected by Cefoxitin disc diffusion test and BD Phoenix automated system (Becton Dickinson, USA). MIC determinations for Vancomycin were performed by using Etest (Biomerieux, France) method according to the manufacturer's recommendations. Quality control testing was performed using ATCC S. aureus 29213 strain.

All isolates were screened for the presence of the hVISA phenotype by Macro Etest (MET) method. According to the manufacturer's recommendations, two hundred microliters of bacterial suspensions with a turbidity equivalent to that of a 2.0 McFarland density standard were spread onto 90-mm brain heart infusion (BHI) agar plates and allowed to dry for 15 minutes. Vancomycin and Teicoplanin Etest strips were applied to the surface of the BHI agar and the plates were read at 48 hours after incubation at 35°C. A strain with a MIC of ≥8 µg/mL for both Vancomycin and Teicoplanin or ≥12 µg/mL for Teicoplanin alone was considered positive for hVISA by MET [4]. The mean MIC and geometric mean MIC were calculated for each year and the differences between years were analyzed with SPSS software, version 16.0 using one-way analysis of variation (ANOVA) and the test of linearity.

Results

The study included 45 MRSA strains of which 14 were isolated in 2012, 10 in 2013, 14 in 2014 and seven in 2015. There were no VRSA or VISA among the isolates. Only one strain (2.2%) was evaluated as hVISA.

Vancomycin MICs distributions for 45 MRSA strains isolated during 2012-2015 and 84 isolates from our previous study conducted between 2007-2011 are shown in Table 1. The mean MICs and geometric mean MICs of Vancomycin for all isolates over the years are shown in Figure 1.

When compared, there were significant differences between the years (2012-2015) for the mean MICs (p=0.027) and the trend in the increase in the Vancomycin mean MICs over the years was found to be significant (p=0.005).

When the results of the previous and recent studies were evaluated together, there were significant differences between the years (2007-2015) for the mean MICs (p=0.001). Although

Table 1. Distribution of Vancomycin MICs for MRSA strains over the years

		MIC (µg/mL)							
Year	No. of strains	0.19	0.50	0.75	1.00	1.50	2.00	Mean MIC±SD	Geometric mean MIC
2007	31	1	1	5	23	1	-	0.93±0.21	0.90
2008	15	-	-	-	13	2	-	1.07±0.18	1.06
2009	21	-	-	-	20	1	-	1.02±0.11	1.02
2010	10	-	-	-	9	1	-	1.05±0.16	1.04
2011	7	-	1	-	3	3	-	1.14±0.38	1.08
2007-11	84	1	2	5	68	8	-	1.01±0.20	0.99
2012	14	-	1	1	12	-	-	0.95±0.14	0.93
2013	10	-	-	1	5	4	-	1.18±0.29	1.14
2014	14	-	-	1	8	5	-	1.16±0.27	1.13
2015	7	-	-	1	2	3	1	1.32±0.43	1.26
2012-15	45	-	1	4	27	12	1	1.12±0.29	1.09
2007-15	129	1	3	9	95	20	1	1.05±0.24	1.02

MIC: Minimum inhibitory concentration; MRSA: Methicillin-resistant Staphylococcus aureus; SD: Standard deviation

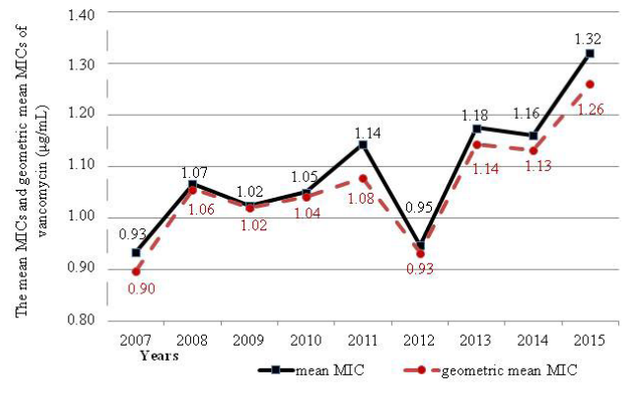

Figure 1. The mean MICs and geometric mean MICs of vancomycin for the isolates over the years

there was an instant decrease in 2012, the upward trend in the Vancomycin mean MICs over the years was found to be significant (p<0.001).

Discussion

S. aureus is one of the most important causes of bacteremia worldwide. In addition to Methicillin resistance, various levels of reduced susceptibility to glycopeptides are of great concern for the utility of Vancomycin and Teicoplanin in these patients. In the Clinical Practice Guidelines for the treatment of MRSA infections by the Infectious Diseases Society of America (IDSA), alternative regimens are suggested for the treatment of infections due to MRSA strains with reduced susceptibility to Vancomycin [1]. In the statement of European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Expert Panel Meeting, it is also recommended that alternative therapies with the combination of Vancomycin and other drugs, or by providing doses of Vancomycin high enough to achieve trough levels >15 mg/L should be used for the subgroup of patients with infections due to strains with Vancomycin MIC values of >1 mg/L. Some evidence suggests that Vancomycin success rate in treating MRSA bacteremia was found to be much higher for isolates with MICs of 0.5 mg/L (56%) than for isolates with MIC values of 1.0-2.0 mg/L (10%) [8].

When we evaluated the mean MIC of Vancomycin for MRSA blood isolates, we found statistically significant difference between the years 2007-2015 (p=0.001) with an upward trend in Vancomycin MIC values (p<0.001).

In the Tigecycline Evaluation and Surveillance Trial (T.E.S.T), 99.92% of the isolates had Vancomycin MICs of ≤2% μg/mL, and 0.08% had MICs of 4-8 μg/mL, with no

VRSA isolates reported. The rate of isolates with MICs of ≥2 μg/mL was increased to 11.2% in 2009, while it was 5.6 % in 2004 [9]. In a university hospital, among 6,002 MRSA isolates, a shift in Vancomycin MICs from <0.5 to 1.0 μg/mL was observed during a 5-year period. The researchers reported that the percentage of S. aureus isolates with a Vancomycin MIC of 1 μg/mL in 2004 was significantly higher than the percentage of isolates in 2000 (70.4% versus 19.9%; p<0.001) [10].

In our study, the increase in mean MICs over the years (2007-2015) was found to be statistically significant. In a study conducted in Mexico, 90% of the isolates were determined to have MIC values of ≥2 μg/mL [11]. Kehrmann et al. assessed the Vancomycin MIC distribution for MRSA blood culture isolates over a period of six years in Germany [12]. They reported that the geometric mean MIC increased by 1.34 fold in city A over the study period (p<0.05), but there was no meaningful change in city B (a 1.09-fold increase, p>0.05). They suggested that the creep phenomenon was a regional problem.

MIC creep doesn't seem to be a universal phenomenon [12]. Some centers noted that there was no change in Vancomycin MICs over the years, in fact, they even reported reductions in Vancomycin MIC values [13,14]. In a study with large numbers of S. aureus isolates from multiple centers, it was reported that center to center heterogeneity leads to a net neutralization effect, with no overall changes in Vancomycin susceptibility observed [13].

The reported prevalence of hVISA ranged from 0% to 74% [7]. The differences are thought to be related to the test method used, the patient population included and diversities in study design. In our study, the hVISA ratio was 2.2% between the years

2012-2015. We found no hVISA in our previous study conducted between the years 2007-2011 [15]. The population analysis profile (PAP)/AUC method is still considered to be the reference method for identifying hVISA phenotype. However, in the majority

of the studies, as well as our study, hVISA was not confirmed by the gold standard method [7]. Another limitation of our study is that we have not determined the clonal relationship between strains.

We observed an increase in Vancomycin MICs for MRSA blood culture isolates over the years at our institution. It is important to monitor local Vancomycin MICs in invasive MRSA isolates systematically and to be aware of reduced Vancomycin susceptibility for a potential failure of Vancomycin treatment.

Competing interests

The authors declare that they have no competing interests.

Human rights statement

The authors declare that they comply with the international guidelines, the "Regulations on Pharmaceutical Research" enforced by The Ministry of Health of Turkey published in the 27089 numbered Official Journal dated 23 December 2008, and the other regulations published later and all procedures performed in studies involving human

participants should be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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